Remarks

Claims 27, 29 and 30 were pending in the subject application. By this Amendment, the applicants have amended claims 27 and 30, canceled claim 29, and added new claims 31-33. Support for the amendments can be found throughout the specification including, for example, claim 11 as originally filed; at page 4, lines 8-10 of the specification; page 5, lines 20-22; page 6, lines 24-26; and Example 1. No new matter has been added by these amendments. Accordingly, claims 27 and 30-33 are currently before the Examiner for consideration. Favorable consideration is respectfully requested.

The amendments presented herein have been made to lend greater clarity to the claimed subject matter and to expedite prosecution of the subject application to completion. These amendments should not be construed as an indication of the applicants' agreement with, or acquiescence to, the rejections of record. Favorable consideration of the claims now presented, in view of the remarks and amendments set forth herein, is earnestly solicited.

Claims 27, 29, and 30 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The applicants respectfully traverse this rejection as it relates to the claims presented herein because the scope and meaning of these claims would be clear to the skilled artisan.

In an effort to expedite prosecution, the applicants have amended claim 27 to more specifically recite "homologous and/or orthologous antigen capture reagents." The applicants respectfully submit that the metes and bounds of the claims as currently presented can be readily understood by one skilled in the art.

The test for definiteness under 35 U.S.C. §112, second paragraph, is whether "those skilled in the art would understand what is claimed when the claim is read in light of the specification." *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986). The applicants respectfully submit that the level of skill in the relevant art (molecular biology) is high and that the skilled artisan would have no difficulty ascertaining the metes and bounds of the claims, particularly the terms "homologous and/or orthologous" when applied to antigens and when read in light of the examples given in the specification as well as the disclosure at page 4, lines 8-11:

> Preferably, the negative control reagent is an entity that has physical, chemical, and/or antigenic properties in common with at least one capture reagent. The common properties may be, for example, molecular weight, charge, solubility, tertiary structure and/or conformation. The negative control reagent may be a homolog, ortholog or other such related molecule to the capture reagent.

The Office Action indicates that the terms "homologous" and "orthologous" can have definite meanings. While this may be true, at least with regard to homologous in a broad sense, the use of these terms with specific reference to antigens is not ambiguous. For example, a search of issued patents finds literally thousands of claims that use the word "homologous." Thus, depending on the context (in this case, antigens), the use of the term "homologous" can be clear and definite. The term "orthologous" is also well-known to the skilled artisan to mean genes found in different species that can be traced to a common ancestral gene (see, for example, orthologous (n.d.), A Dictionary of Biology, 2004, Retrieved Feb. 1, 2010 from http://www.encyclopedia.com/doc/1O6-orthologous; ortholog. (n.d.). Dictionary.com's 21st Century Lexicon, Retrieved Jan. 29, 2010 from http://dictionary.reference.com/browse/ortholog; and ortholog, Retrieved Jan. 29, 2010 from http://en.wikipedia.org/wiki/Ortholog#Orthology).

In the current case, where the specification provides guidance and examples (e.g. HLA antigens), and the claims are specifically limited to a narrow context (i.e. antigens), the scope and meaning of the claims are clear and definite.

It is well established that "definiteness of the language employed must be analyzed – not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art." *In re Moore*, 439 F.2d 1232, 1235 (CCPA 1971). As noted above, the specification sets out and provides examples of what is meant by "homologous" and "orthologous" antigen capture reagents. This, when read in light of known definitions of the terms "homologous" and "orthologous" in the context of antigens, provides an adequate notification of the metes and bounds of what is being claimed.

Accordingly, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 USC §112, second paragraph.

Claims 27, 29, and 30 have been rejected under 35 U.S.C. §102(b) as being anticipated by Hoffman *et al.* (U.S. Patent No. 5,599,543). The applicants respectfully traverse this rejection because the Hoffman *et al.* reference does not disclose each and every step of the applicants' advantageous multi-analyte assay wherein a negative control is generated using the assayed sample.

In order to anticipate, a single prior art reference must disclose within its four corners, each and every element of the claimed invention. In *Lindemann v. American Hoist and Derrick Co.*, 221 USPQ 481 (Fed. Cir. 1984), the court stated:

> Anticipation requires the presence in a single prior art reference, disclosure of each and every element of the claimed invention, arranged as in the claim. *Connell v. Sears Roebuck and Co.*, 722 F.2d 1542, 220 USPQ 193 (Fed. Cir. 1983); *SSIH Equip. S.A. v. USITC*, 718 F.2d 365, 216 USPQ 678 (Fed. Cir. 1983). In deciding the issue of anticipation, the [examiner] must identify the elements of the claims, determine their meaning in light of the specification and prosecution history, and identify corresponding elements disclosed in the allegedly anticipating reference. *SSIH, supra*; *Kalman [v. Kimberly-Clarke*, 713 F.2d 760, 218 USPQ 781 (Fed. Cir. 1983)] (emphasis added). 221 USPQ at 485.

The Hoffman *et al.* reference describes a study in which blood sera from residents of malarious areas were tested for antibody activity against antigens from common forms of human malaria (*P. vivax* circumsporozoite (CS) protein and *P. falciparum* CS protein) as well as against a ***positive control*** peptide from the CS protein of the murine malarial parasite *P. yoelii* (SEQ ID NO:7). See, for example, col. 7, lines 35-40 and lines 46-49, referencing SEQ ID NO:7 as a positive control and wherein the binding activity of the positive control was compared with that of the binding activities of the human malaria.

As understood by the skilled artisan, a positive control is expected to provide a positive result and acts as a standard against which to measure differences in severities among experimental groups. A positive control confirms that a procedure is competent in observing the effect (therefore minimizing false negatives). In contrast, a negative control is provided to ensure that an unknown variable is not adversely affecting the experiment, which might result in

a false-positive conclusion. The applicants respectfully submit that, having read Hoffman *et al.* and understanding the difference between positive controls and negative controls, the skilled artisan would recognize that the "peptide circumsporozoite protein repeat regions of different parasite species" in the reference of Hoffman *et al.* (*e.g.*, col. 7) were used not as a negative control but rather a positive control.

Further, Hoffman *et al.* fail to teach the step of identifying the least reactive capture reagent as a negative control. What Hoffman *et al.* considered as their *negative control* was described at col. 7, lines 40-45 and lines 57-59 and Table 3. Specifically, Hoffman's "negative serum controls" were *wholly separate assays* conducted on persons with no history of exposure to malaria or "naïve" persons. These assays served as negative controls to those assays conducted on test samples from individuals exposed to malaria (see "Study Population" in col. 6, lines 53-63). As taught by the subject application, "[p]roblems may arise due to the fact that the source of the negative samples is different from that of the...sample [being assayed], resulting in unexpected reactivity." See, p. 2, line 29 through p. 3, line 2. Thus, Hoffman *et al.* teach negative controls that are quintessential examples of the problem being addressed by the applicants' claimed invention.

Contrary to the Hoffman *et al.* negative controls, the subject application recites claims in which a negative control is determined by measuring the reactivity of a sample toward antigen capture reagents attached to a support and identifying the least reactive capture reagent to the ***same*** sample as the negative control. In fact, the subject specification emphasizes that it is advantageous to select a negative control from the results obtained ***only with the same sample biological material being assayed*** because it obviates the step of processing a separate negative control material and addresses any problems that may arise related to unexpected reactivity to unrelated samples used as negative controls. See, p. 3, lines 1-2, 11-13 and 25-28.

Hoffman *et al.* do not disclose or suggest an assay wherein a negative control is generated via assessment of the least reactive binding reactions to a capture reagent within the ***same*** assayed sample (sera) as the negative control. Therefore, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §102(b) based on the Hoffman *et al.* reference.

Claims 27, 29, and 30 have been rejected under 35 U.S.C. §102(b) as being anticipated by Geyson *et al.* (Proc. Natl. Acad. Sci. USA 81:3998, 1984). The applicants respectfully traverse this rejection because the Geyson *et al.* reference does not disclose each and every step of the claimed assay.

As currently claimed, the present invention requires the assayed sample to be that of blood, tissue, or urine sample and that the antigen capture reagents be homologous and/or orthologous. Nowhere in the Geyson *et al.* reference is there a description or even suggestion to assay a blood, tissue or urine serum sample. Further, the Geyson *et al.* capture agents are not homologous or orthologous antigen capture agents.

Geysen *et al.* teach the use of enzyme-linked immunoassays (ELISA) in identifying an immunogenic epitope of an important protein (VP1) of foot-and-mouth disease virus (FMDV, type O_1). To do so, Geysen *et al.* created several hundred support panels, one for each of the 208 possible hexapeptides from the amino acid sequence of the VP1 protein of FMDV type O_1 (see excerpt from Figure 1: "[t]he 213-amino acid sequence of VP1 (FMDV, type O_1)...was subdivided into hexapeptide units, and each was synthesized on a *separate* polyethylene support...." and description under "Synthesis of Peptides." The applicants respectfully submit that the skilled artisan, having read Geysen *et al.*, would never have considered subdivided hexapeptide units of VP1 to be homologous or orthologous antigens.

In addition, the antisera against which each panel of hexapeptide unit was tested were isolated virus-bound antibodies (see, description under "Antisera" and lines 6-10 of 2nd col. on page 3999). Such samples are not blood, tissue, or urine serum samples as recited in the claims as amended herein.

New claims 31-33 recite blood, tissue, or urine sera samples to be tested against human leukocyte antigens (HLAs). The applicants respectfully submit that nowhere in Geysen *et al.* is there a description to use HLAs as capture reagents.

Finally, the applicants submit that none of the assays performed by Geysen *et al.* using their multitude of hexapeptide units were used in identifying a negative control. Rather, Geyson *et al.* used the normal or average binding reactions, as opposed to the ***least*** binding reaction, of the hexapeptide units being tested in their sample as negative controls in their test (p.4000,

section 3 of the Discussion, "*Except* for cases in which either all or *none* of the peptides react, a large number of the peptides would effectively act as negative controls in the test. With adjacent peptides sharing a common sequence of five amino acids, the observation of peaks *above a generally uniform background level* would indicate a valid test." Geysen *et al.* reason that by interpreting the data in this fashion, one can more readily identify the most reactive peptides as a possible epitope of VP1.

Thus, Geyson *et al.* do not disclose each and every limitation of the claimed invention. The applicants' use of: blood, tissue, or urine serum samples, as well as homologous and/or orthologous antigen capture agents, and the least reactive capture reagent of an assay as a negative control, differentiates the invention from the experiments conducted by Geysen *et al.* Therefore, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §102(b) based on the Geysen *et al.* reference.

In view of the foregoing remarks and the amendment above, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

The applicants also invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephone interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

David Saliwanchik

David R. Saliwanchik
Patent Attorney
Registration No. 31,794
Phone: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

DRS/la